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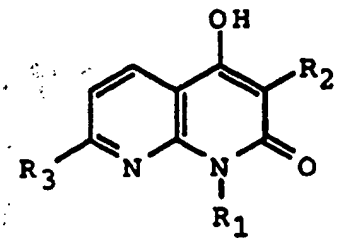
(54) Title: NAPHTHYRIDINE DERIVATIVES

(57) Abstract

Compounds of formula (I) including pharmaceutically acceptable salts thereof in which R_1 represents a C_{1-6} alkyl group; R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-5} alkyl group; and R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-5} alkyl group are disclosed, which are antirheumatic agents and are useful as modulators of cytokine synthesis, immunomodulatory agents, anti-inflammatory agents and anti-allergic agents. Compositions containing these compounds and processes to make these compounds are also disclosed.



(I)

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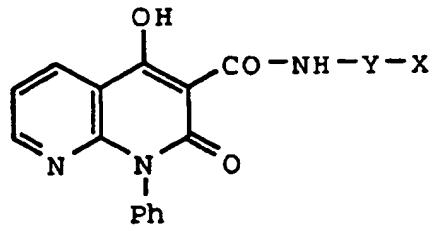
NAPHTHYRIDINE DERIVATIVES

The present invention relates to therapeutic agents and, in particular, to dialkyl 8-alkyl-5-hydroxy-7-oxo-1,8-naphthyridine-2,6-dicarboxylates, to processes for their preparation, to pharmaceutical compositions containing them and to their therapeutic activity as anti-rheumatic agents.

Rheumatoid arthritis is currently treated with anti-inflammatory agents, which alleviate the symptoms but do not affect the progression of the condition, or with disease-modifying antirheumatic drugs e.g. gold compounds, D-penicillamine, sulphasalazine, azathioprine and methotrexate. However, most disease-modifying antirheumatic drugs are associated with side-effects, often of a serious nature. This means that such drugs are often only used as a last resort in the most serious cases. Consequently a need exists for a less toxic, disease-modifying, antirheumatic drug which may be administered orally.

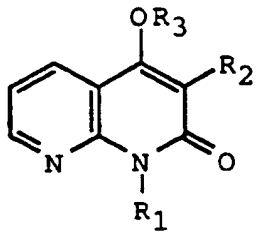
EP 452,873 discloses the use of substituted 1-aryl-1,8-naphthyridine-3-carboxamides of formula A



A

in which X represents hydrogen, a C_{1-6} alkyl group, aralkyl, aryl, an aromatic heterocyclic group etc. and Y represents a single bond or alkylene, as antiinflammatory agents which are useful in the treatment of rheumatoid arthritis.

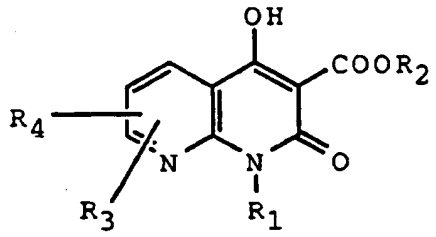
Japanese Patent Application 52-116495 (1977) discloses compounds of formula B



B

in which R_1 represents an alkyl group (optionally substituted), an alkenyl group or an aryl group; R_2 represents hydrogen, an alkyl group (optionally substituted) or an aryl group and R_3 represents hydrogen or an acyl group, which allegedly possess analgesic, antiinflammatory, central nervous system depressant and diuretic effects. There is no suggestion in this document that the compounds have any anti-rheumatic activity.

US 4,128,649 discloses compounds of formula C

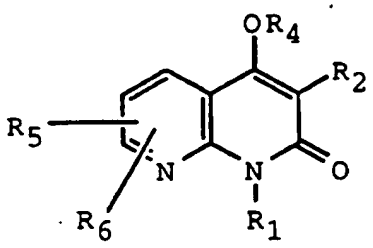


C

wherein R_1 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl etc; R_2 represents hydrogen, a C_{1-4} alkyl group, a C_{3-6} alkenyl group or a C_{3-6} alkenyl group; R_3 and R_4 independently represent hydrogen or a C_{1-4} alkyl group and/or salts thereof. Ethyl 4-hydroxy-1,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate is one of fourteen compounds specifically exemplified. The use of these compounds as anti-allergic agents is also disclosed. There is no

suggestion in this document that the compounds have any anti-rheumatic activity.

US 4,215,123 discloses a method of treating peptic ulcers comprising the administration of a compound of formula D

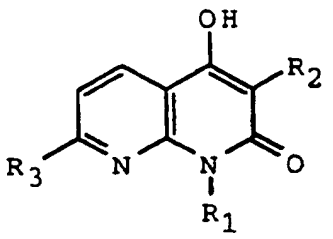


D

wherein R_1 represents hydrogen, a C_{1-6} alkyl group, a C_{7-9} aralkyl group etc; R_2 represents hydrogen, a C_{2-7} alkoxycarbonyl group, carboxy, carbamoyl, C_{2-7} N-alkylcarbamoyl etc; R_4 is hydrogen or a C_{1-6} alkyl group and R_5 and R_6 are independently hydrogen or a C_{1-6} alkyl group or an alkali metal salt thereof. Ethyl 4-hydroxy-1,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate and ethyl 1-ethyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate are specifically exemplified. There is no suggestion in this document that the compounds have any anti-rheumatic activity.

In addition ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate is disclosed without any pharmacological activity in J. Med. Chem. 1987, 30, 2270, in which the structure activity relationships of these compounds are discussed.

The present invention provides compounds of formula I



I

including pharmaceutically acceptable salts thereof in which

R_1 represents a C_{1-6} alkyl group;

R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-5} alkyl group; and

R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-5} alkyl group.

It will be understood that a group containing a chain of 3 or more carbon atoms may be straight or branched, for example, propyl includes n-propyl and isopropyl and butyl includes n-butyl, sec-butyl, isobutyl and tert-butyl. The total number of carbon atoms is specified for certain substituents, for example C_{2-6} alkoxycarbonyl refers to an alkoxycarbonyl group having from two to six carbon atoms.

A compound of formula I will generally exist in equilibrium with its other tautomeric forms. It is to be understood that all tautomeric forms of the compounds of formula I, as well as mixtures thereof, are included within the scope of the present invention.

In a preferred group of compounds of formula I,

R_1 represents a C_{1-4} alkyl group (for example methyl, ethyl, propyl and butyl);

R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-3} alkyl group (for example R_2 represents methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl); and

R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-3} alkyl group (for example R_3 represents methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl).

In a more preferred group of compounds of formula I, R_1 represents a C_{1-2} alkyl group and R_2 and R_3 are identical and represent a C_{2-4} alkoxycarbonyl group.

A specific compound of formula I is:

diethyl 5-hydroxy-8-methyl-7-oxo-7,8-dihydro-1,8-naphthyridine-2,6-dicarboxylate

and pharmaceutically acceptable salts thereof.

Compounds of formula I may contain one or more chiral centres and exist in different optically active forms. When a compound of formula I or a salt thereof contains a single chiral centre (for example when R_1 represents sec-butyl) it may exist in two enantiomeric forms. The present invention includes individual enantiomers and mixtures of those enantiomers. The enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include resolution via formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; resolution via formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer by reaction with an enantiomer-specific reagent, for example, enzymatic esterification, oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent.

It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation processes described above, at least one further step will subsequently be required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I or a salt thereof contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example, chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I or II and mixtures thereof.

Some compounds of formula I may exist in the form of solvates, for example, hydrates, which also fall within the scope of the present invention.

The compounds of formula I may form organic or inorganic salts, for example, the compounds of formula I may form acid addition salts with inorganic or organic acids, e.g. hydrochloric acid, hydrobromic acid, fumaric acid, tartaric acid, citric acid, sulphuric acid, hydriodic acid, maleic acid, acetic acid, succinic acid, benzoic acid, pamoic acid, palmitic acid, dodecanoic acid and acidic amino acids such as glutamic acid. Some compounds of formula I may form base addition salts, for example, with alkali metal hydroxides for example sodium hydroxide, with aminoacids for example, lysine or arginine or with organic bases, for example meglumine. It will be appreciated that such salts, provided they

are pharmaceutically acceptable may be used in therapy in place of the corresponding compounds of formula I. Such salts are prepared by reacting the compound of formula I with a suitable acid or base in a conventional manner. Such salts may also exist in form of solvates (for example, hydrates).

Certain compounds of formula I or salts thereof may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

The present invention also provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I including pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable diluent or carrier. Such pharmaceutical formulations may be used in the treatment of rheumatic diseases for example rheumatoid arthritis or osteoarthritis.

As used hereinafter, the term "active compound" denotes a compound of formula I including pharmaceutically acceptable salts thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally, topically, ocularly, aurally, nasally, intravaginally or to the buccal cavity, to give a local and/or systemic effect. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy.

The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions.

Tablets may be prepared from a mixture of the active compound with fillers such as lactose or calcium phosphate, disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate, binders for example microcrystalline cellulose or polyvinyl pyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethyl-cellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate.

Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 0.1 to 1000 mg (for example

10 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg or 800 mg) of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example sunflower oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions for topical administration are also preferred compositions of the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the

compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as described above, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with hard fat, synthetic glycerides or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions of the invention suitable for inhalation via the mouth and/or the nose are the known pharmaceutical forms for such administration, for example aerosols, nebulised solutions or powders. Metered dose systems, known to those skilled in the art, may be used.

Compositions suitable for application to the buccal cavity include slow dissolving tablets, troches, chewing gum, gels, pastes, powders, mouthwashes or rinses.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion, or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be a) liquid such as an oily solution or suspension of the compound to be infused for example in the form of a

very sparingly water-soluble derivative such as a dodecanoate salt or b) solid in the form of an implanted support for example of a synthetic resin of waxy material for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients, for example, a non-steroidal antiinflammatory agent e.g. ibuprofen, S(+)-ibuprofen, flurbiprofen or S(+)-flurbiprofen, an analgesic or an antipyretic agent.

The compounds of formula I are indicated for use as medicaments. In particular compounds of formula I are indicated for use as anti-rheumatic agents by their activity demonstrated by means of tests on standard laboratory animals. Such tests include, for example, the oral administration of compounds of formula I to mice with experimental antigen-induced arthritis. Compounds of formula I are suitable for use in treating rheumatic diseases for example rheumatoid arthritis, osteoarthritis, osteoporosis, crystal arthropathies (e.g. gout), reactive arthritis, ankylosing spondylitis or psoriatic arthropathy. It is believed that compounds of formula I and pharmaceutically acceptable salts thereof are disease-modifying antirheumatic agents.

The compounds of formula I are also indicated for use as immunomodulatory agents, and are generally

immunosuppressants. The compounds according to the invention are useful in the treatment of diseases resulting from an aberrant immune reaction. Thus the pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat diseases with an immunological association. The compounds are also useful to treat immunologically-induced diseases including allergic and inflammatory conditions, particularly those mediated by the release of cytokines such as tumour necrosis factor (TNF).

The immunomodulatory activity of compounds falling within formula I may be demonstrated by means of in vitro and in vivo tests. Such tests include, for example, in vitro and/or in vivo tests which detect the production of inflammatory cytokines e.g. TNF, in response to endotoxins. Thus, compounds of formula I are useful as modulators of cytokine synthesis, immunomodulatory agents, anti-inflammatory agents and anti-allergic agents.

Diseases which may be treated by compounds according to the present invention include immunologically based diseases such as transplant rejection, eg kidney rejection; and graft-versus-host disease; joint inflammation; autoimmune diseases, such as thyroiditis, type 1 diabetes, multiple sclerosis, cerebral inflammation, sarcoidosis and systemic lupus erythematosus; cutaneous disorders, such as contact sensitivity, eczema and psoriasis; respiratory disorders for example: asthma and rhinitis; gastrointestinal disorders for example: gastritis, Crohn's disease, ulcerative colitis and other inflammatory diseases of the bowel; diseases of the oral cavity for example: periodontitis and gingivitis; HIV infection (AIDS); septic shock; malaria; cerebral inflammation; viral diseases; neoplasia and cachexia. Other diseases which

may also be treated by compounds of the present invention include muscle trauma, gout, tendonitis and bursitis; Alzheimer's disease; cutaneous disorders for example: urticaria, allergic skin diseases, burns, occular inflammation and iritis.

Compounds of formula I may also be suitable for the treatment of diseases of the oral cavity for example periodontitis, gingivitis and alveolar bone resorption.

Accordingly, in a further aspect, the present invention also includes a method of treating rheumatic diseases, particularly rheumatoid arthritis and osteo-arthritis, comprising the administration of a therapeutically effective amount of a compound of formula I including pharmaceutically acceptable salts thereof to a mammal in need thereof.

Accordingly, in another aspect, the present invention also includes a method of treating diseases with an immunological association in a mammal in need of such treatment, comprising the administration of a therapeutically effective amount of a compound of formula I to said mammal.

Compounds of formula I may also be administered in a prophylactic manner to mammals, particularly humans who have been identified as being susceptible to arthritic diseases.

Whilst the precise amount of active compound administered will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, a suitable dose for oral administration to mammals, including humans, is generally within the range

0.01-80 mg/kg/ day, more usually 0.2-40 mg/kg/day given in single or divided doses. For parenteral administration, a suitable dose is generally within the range 0.001-80 mg/kg/day, more usually 0.2-40 mg/kg/day given in single or divided doses or by continuous infusion. A suitable preparation for topical administration generally contains the active ingredient within the range 0.01-20% by weight, more usually 0.05-5% by weight. Oral administration is preferred.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat rheumatic diseases such as rheumatoid arthritis and osteoarthritis. In such treatment the amount of the compound of formula I administered per day is in the range 0.1 to 6000 mg.

In yet another aspect, the present invention provides the use of a compound of formula I in the manufacture of a medicament for use in the treatment of a rheumatic disease such as rheumatoid arthritis and osteoarthritis.

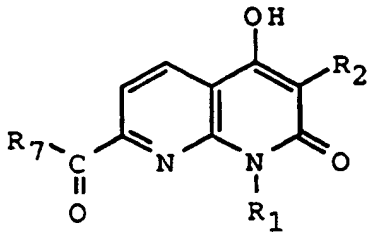
The present invention also includes a method of treating inflammatory and/or allergic conditions in a mammal in need of such treatment comprising the administration of a therapeutically effective amount of a compound of formula I to said mammal.

In yet another aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for use in the treatment of inflammatory diseases, allergic conditions or diseases with an immunological association.

Processes for the preparation of compounds of formula I will now be described. These processes form a

further aspect of the present invention. The processes listed are preferably carried out at atmospheric pressure unless otherwise stated.

Compounds of formula I may be prepared by reacting a compound of formula IIa



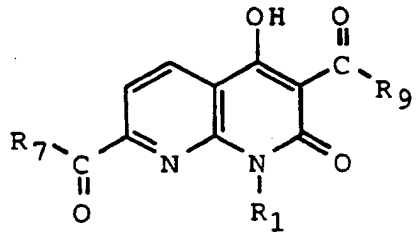
IIa

in which R_1 and R_2 are as previously defined and R_7 represents a leaving group for example halo, a (C_{1-6} alkoxy)carbonyloxy group or a C_{1-5} alkoxy group with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example pyridine, and optionally when R_7 represents halo in the presence of a base, for example triethylamine.

Compounds of formula I may be prepared by reacting a compound of formula IIa in which R_1 and R_2 are as previously defined and R_7 represents hydroxy with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example excess R_5OH, and/or in the presence of: a) an acid catalyst, for example toluene-4-sulphonic acid; or b) a dehydrating agent, for example

concentrated sulphuric acid or a carbodiimide; or c) an organic liquid which provides a method of water removal by formation of an azeotrope, for example toluene.

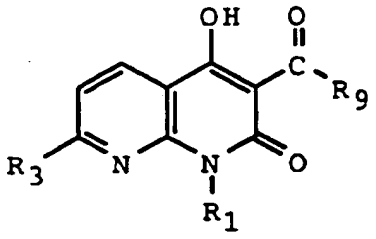
Compounds of formula I in which R_2 and R_3 are identical and represent a group of formula $COOR_4$ as previously defined may be prepared by reacting a compound of formula IIb



IIb

in which R_1 is as previously defined and R_7 and R_9 independently represent a) a leaving group for example halo, a (C_{1-6} alkoxy)carbonyloxy group or a C_{1-5} alkoxy group, or b) hydroxy, with an alcohol of formula R_4OH in which R_4 represents a C_{1-5} alkyl group at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, optionally when R_7 and/or R_9 represents halo in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example pyridine, and/or in the presence of a base, for example triethylamine; and optionally: when R_7 and/or R_9 represents hydroxy in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example excess R_4OH, and/or in the presence of: a) an acid catalyst, for example toluene-4-sulphonic acid; or b) a dehydrating agent, for example concentrated sulphuric acid or a carbodiimide; or c) an organic liquid which provides a method of water removal by formation of an azeotrope, for example toluene.

Compounds of formula I may be prepared by reacting a compound of formula IIc

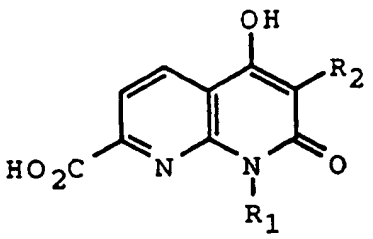


IIc

in which R_1 and R_3 are as previously defined and R_9 represents a leaving group for example halo, a (C_{1-6} alkoxy)carbonyloxy group or a C_{1-5} alkoxy group, with an alcohol of formula R_4OH, in which R_4 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, and optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example pyridine, and optionally when R_9 represents halo in the presence of a base, for example triethylamine.

Compounds of formula I may be prepared by reacting a compound of formula IIc in which R_1 and R_3 are as previously defined and R_9 represents hydroxy, at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example excess R_4OH, and/or in the presence of: a) an acid catalyst, for example toluene-4-sulphonic acid; or b) a dehydrating agent, for example concentrated sulphuric acid or a carbodiimide; or c) an organic liquid which provides a method of water removal by formation of an azeotrope, for example toluene.

Preferably compounds of formula I may be prepared by reacting a compound of formula IId



IId

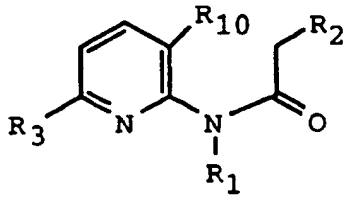
in which R_1 and R_2 are as previously defined with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, preferably by heating at a temperature in the range 20-150°C, optionally in the presence of an inert organic liquid which is preferably a solvent of the reactants, for example excess R_5OH, in the presence of: a) an acid catalyst, for example toluene-4-sulphonic acid; or b) a dehydrating agent, for example concentrated sulphuric acid or a carbodiimide; or c) an organic liquid which provides a method of water removal by formation of an azeotrope, for example toluene.

It will be appreciated by those skilled in the art that when R_7 and/or R_9 represents a C_{1-5} alkoxy group in IIa, IIb or IIc then an equilibrium will be established in a transesterification reaction from which the desired product may be obtained by normal separation methods for example crystallisation or chromatography. Preferably R_7OH and R_9OH are more volatile than R_5OH and R_4OH, respectively, and may be removed by distillation so that the equilibrium favours the desired product.

It will be appreciated by those skilled in the art that, in the preparation of compounds of formula I from compounds of formulae IIa, IIc or IId, undesirable transesterification reactions may occur if the alkoxy group in either R_2 or R_3 is not identical to R_4O- or

R_5O-. The desired products may be obtained by normal separation methods for example crystallisation or chromatography.

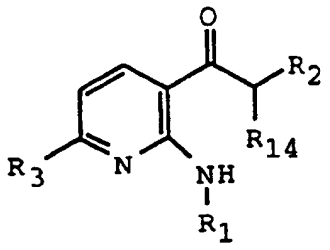
Compounds of formula I may be prepared by cyclising a compound of formula III



III

in which R_1, R_2 and R_3 are as initially defined and R_{10} represents cyano or a group of formula COR_{11} in which R_{11} represents a leaving group, for example halo, a C_{1-6} alkoxy group, an aryloxy group, an arylalkoxy group, a C_{1-6} alkanoyloxy group, a (C_{1-6} alkoxy)carbonyloxy group, an amino group of formula $NR_{12}R_{13}$ (in which R_{12} and R_{13} independently represent hydrogen or a C_{1-6} alkyl group or R_{12} and R_{13} together with the nitrogen atom to which they are attached represent a saturated 3-7 membered heterocyclic ring optionally containing sulphur, oxygen or an additional nitrogen atom, wherein the ring is optionally substituted by one or more C_{1-4} alkyl groups), in the presence of a base, for example sodium hydride or sodium ethoxide, in the presence of an inert organic liquid which is preferably a solvent for the compound of formula III, for example ethanol, tetrahydrofuran or N,N-dimethylformamide, at a temperature in the range -50 to 250°C, preferably in the range -15 to 150°C, optionally followed by hydrolysis when R_{10} represents cyano and optionally followed by acidification.

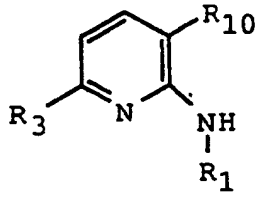
Compounds of formula I may be prepared by cyclising a compound of formula IV



IV

in which R_1, R_2 and R_3 are as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously defined, for example by heating, at a temperature in the range 30-250°C preferably in the presence of an inert organic liquid which is preferably a solvent for the compound of formula IV, for example N,N-dimethylformamide.

Compounds of formula I may be prepared by condensing a compound of formula V



V

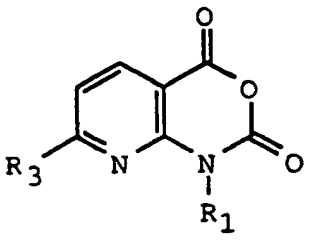
in which R_1, R_3 and R_{10} are as initially defined with a compound of formula VI

$$R_2CH_2R_{14} \qquad \text{VI}$$

in which R_2 is as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously defined, for example by reacting together at a temperature in the range 0-150°C, preferably in the presence of a base, for example sodium ethoxide, in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example

N,N-dimethylformamide, and then reacting at a temperature in the range 0-250°C, optionally followed by hydrolysis when R_{10} represents cyano and optionally followed by acidification. Preferably R_{14} is the same as the group R_2.

Compounds of formula I may be prepared by reacting a compound of formula VII



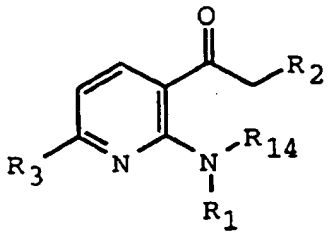
VII

in which R_1 and R_3 are as initially defined with a compound of formula VI

$$R_2CH_2R_{14} \qquad \text{VI}$$

in which R_2 is as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously defined, for example by reacting together at a temperature in the range 0-150°C, preferably in the presence of a base, for example sodium hydride, in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example N,N-dimethylformamide, and then reacting at a temperature in the range 0-250°C, optionally followed by acidification. Preferably R_{14} is the same as group R_2.

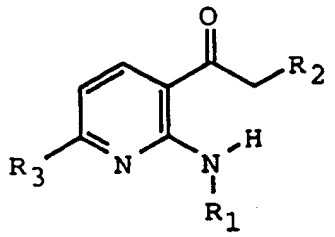
Compounds of formula I may be prepared by cyclising a compound of formula IX



IX

in which R_1, R_2, R_3 and R_{14} are as previously defined, optionally in the presence of a base, for example sodium hydride, preferably in the presence of an organic liquid which is preferably a solvent for the compound of formula IX, for example N,N-dimethylformamide, at a temperature in the range 0-150°C optionally followed by acidification.

Compounds of formula I may be prepared by reacting a compound of formula XIII

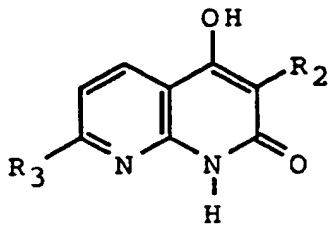


XIII

in which R_1, R_2 and R_3 are as initially defined with a compound of formula Y_1COY_2 in which Y_1 represents halo, alkoxy (optionally substituted by halo), aryloxy, arylalkoxy, cyano or a group of formula $NR_{15}R_{16}$ (in which R_{15} and R_{16} independently represent a C_{1-6} alkyl group or R_{15} and R_{16} together with the nitrogen atom to which they are attached represent a saturated 3-7 membered heterocyclic ring) and Y_2 represents halo, alkoxy (optionally substituted by halo), aryloxy or arylalkoxy (for example Y_1COY_2 is ethyl chloroformate or diethyl carbonate), optionally in the presence of a

base, for example sodium hydride or triethylamine, preferably in the presence of an inert organic liquid which is preferably a solvent for the compound of formula XIII, for example N,N-dimethylformamide, at a temperature in the range 0-150°C.

Compounds of formula I may be prepared by reacting a compound of formula XII



XII

in which R_2 and R_3 are as initially defined, with an alkylating agent of formula R_1X in which R_1 is as previously defined and X represents a leaving group, for example chloro, bromo or iodo. It will be appreciated by those skilled in the art that an O-alkylated or an O,N-dialkylated product may be obtained in this process from which the desired compound may be obtained by chromatography. The undesired O,N-dialkylated product may be converted into the N-alkylated product by methods known to those skilled in the art, e.g. by hydrolysis. Alternatively the O-alkylated product may be converted into the N-alkylated product by heating.

Compounds of formula IIa, IIb, IIc and IId may be prepared by methods analogous to those described for the preparation of compounds of formula I from compounds of formula III, IV, V, VII and IX.

Compounds of IIa, IIb and IIc in which R_7 and/or R_9 are other than hydroxy may also be prepared from compounds of formula IIa, IIb and IIc, respectively, in

which R_7 and/or R_9 represent hydroxy by methods known to those skilled in the art.

It will be appreciated by those skilled in the art that in the processes described above for the preparation of compounds of formula I and IIa, IIb and IIc, in which an ester group is present as a reactive functional group in the starting material, that R_3 may interfere and cause competing side reactions to occur. The desired product may be obtained by separation methods known to those skilled in the art, for example recrystallisation or chromatography.

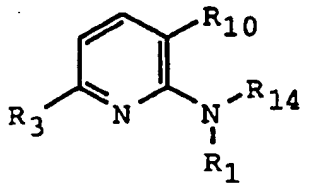
Compounds of formula III may be prepared by reacting a compound of formula V with a compound of formula VI at a temperature in the range -50 to 150°C, preferably in the presence of an organic liquid which is preferably a solvent for the compound of formula V. It will be appreciated by those skilled in the art that R_{14} is preferably more reactive to amination than R_2 otherwise competing side reactions may occur.

Compounds of formula IV may be prepared by reacting a compound of formula V with a compound of formula VI in the presence of a base, for example sodium hydride or sodium ethoxide, in the presence of an organic liquid, preferably a solvent for compounds of formula V, at a temperature in the range -50 to 150°C.

Compounds of formula IV may also be prepared by reacting a compound of formula VII with a compound of formula VI in the presence of a base, for example sodium hydride or sodium ethoxide, in the presence of an organic liquid, preferably a solvent for compounds of formula V, at a temperature in the range -50 to 150°C.

Compounds of formulae V, VI, and VII may be prepared by methods known to those skilled in the art.

Compounds of formula IX may be prepared by reacting a compound of formula X



X

in which R_1, R_3, R_{10} and R_{14} are as defined initially with a compound of formula XI

$$(R_2CH_2)_nM_1 \qquad \text{XI}$$

in which R_2 is as initially defined and when n is 1 then M_1 represents Li or MgX, in which X represents bromo, chloro or iodo, and when n is 2 then M_1 represents Cd, optionally in the presence of a transition metal or a transition metal salt, by methods known to those skilled in the art, optionally followed by hydrolysis when R_{10} represents cyano and optionally followed by acidification.

Compounds of formula X and XI may be prepared by methods known to those skilled in the art. For example, compounds of formula X may be prepared from compounds of formula V.

Compounds of formula XII may be prepared by methods analogous to those described for the preparation of compounds of formula I by reaction of compounds of formulae III, IV, V, VII and IX in which R_1 represents hydrogen.

Compounds of formula XIII may be prepared by reacting a compound of formula V with a compound of formula XI in an analogous manner to the preparation of compounds of formula IX.

Certain intermediate compounds of formulae III, IV, V, VII, IX, X and XII are believed to be novel. All novel compounds herein form a further aspect of the invention.

The therapeutic activity of the compounds of the present invention has been demonstrated by tests which include the oral administration of the compounds to mice with experimental antigen-induced arthritis. The compounds showed activity in the following test.

Experimental Antigen-Induced Arthritis Test

Female BALB/c mice, 8 weeks of age were used: each control group contained either 35, 60 or 80 mice and each test group contained either 13, 15 or 20 mice respectively. The mice were sensitised by subcutaneous injection into the flank or nuchal area with an emulsion (0.1 ml) consisting of a solution of methylated bovine serum albumin (m-BSA) (0.1 mg) in sterile aqueous sodium chloride solution (0.05 ml; 0.15 M) and Freund's Complete Adjuvant (0.05 ml) containing, in total, killed Mycobacterium tuberculosis (0.075 mg). Simultaneously each mouse was injected intraperitoneally with an aqueous suspension of heat killed Bordetella pertussis (0.05 ml; 2×10^9 organisms). Identical injections were administered after 7 days. After a further 14 days the left knee-joint of each mouse was injected with a solution of m-BSA (0.1 mg) in aqueous sodium chloride solution (0.01 ml; 0.15 M) (intra-articular challenge). This procedure induced a chronic erosive arthritis restricted to the challenged joint.

The test compounds were suspended in a vehicle of aqueous carboxymethyl cellulose solution (0.25% w/v) containing TWEEN®80 (1.5% w/v) at varying dosages and 0.1 ml was administered to each test mouse by gastric intubation. The control mice received the vehicle with no test compound. Administration occurred daily for 28 days commencing 14 days after intra-articular challenge. After 42 days the test was terminated and the animals were killed using a rising concentration of carbon dioxide and the arthritic hind leg removed.

The femur and tibia were cut midway along their length and the knee-joint trimmed free of skin and musculature. The arthritic joints were placed in perforated plastic holders and fixed in 10% formol saline for at least 48 hours. They were then decalcified in 5% formic acid for 72 hours with constant agitation (replacing the formic acid after the first 24 hours), washed in water, dehydrated in alcohol and embedded in paraffin wax. The joints were sectioned in the sagittal plane at 5 µm and stained with Van Gieson's stain. Each joint was sectioned at two levels.

The severity of arthritis was assessed by examination of the prepared sections. Synovitis and pannus formation were graded on a 0-5 scale, by a skilled operator, according to the degree of synovial lining cell hypertrophy and hyperplasia, infiltration of the synovium by lymphocytes, plasma cells, monocytes/macrophages, fibroblasts and polymorpho-nuclear (PMN) leukocytes and the degree of pannus formation. Erosions of cartilage and bone were also graded on a 0-5 scale, by a skilled operator, the score reflecting the proportion of articular surface eroded as well as the depth of the erosions. Using the combined data the drug effects were expressed as the percentage change in the mean scores for synovitis and erosions

compared to those of the control group. The data were then analysed using the Mann-Whitney U-test.

Those compounds which induced a statistically significant suppression of erosions or synovitis at a dosage of 30 mg/kg or below were deemed to be active. The results obtained are given in the Examples. Preferred compounds induce a statistically significant suppression of erosions.

The therapeutic activity of compounds of formula I (in particular their ability as immunomodulants) may be demonstrated by activity of certain compounds of formula I (those compounds so tested referred to hereinafter as Test Compounds) in the mouse tumour necrosis factor-α (TNF-α) test (hereinafter referred to as the MTNF Test).

Mouse Tumour Necrosis Factor-α Test

The therapeutic activity of Test Compounds may be demonstrated in an in vivo test which determined the ability of the Test Compounds to inhibit the release of TNF-α in response to the administration of endotoxin. TNF-α is currently thought to be a key mediator in the pathogenesis of a number of autoimmune and inflammatory diseases and its inhibition is a potentially beneficial pharmacological goal. The MTNF Test is similar to that described by Zuckerman and Bendele (1989), Infection and Immunity, Vol 57 (10), pages 3009-3013. The MTNF Test was carried out as described below.

Six week old, barrier-reared female mice of the BALB/c strain were obtained from Harlan-Olac Ltd and maintained under semi-barrier conditions with free access to food (CRM diet) and water for one to three weeks before use. The Test Compound was combined with a

carrier of 100 µl of a solution of 1.5% v/v sorbitan esters (available commercially under the trade name Tween 80) and 0.25% v/v cellosize in sterile water. The Test Compound in the carrier was administered orally to four BALB/c mice (hereinafter referred to as the Test Mice). The concentration of the Test Compound was such as to provide dosages of Test Compound selected from 100 mg/kg, 30 mg/kg, 10 mg/kg, 3 mg/kg, 1 mg/kg, 0.1 mg/kg and 0.03 mg/kg. An endotoxin, (lipopolysaccharide) (hereinafter referred to as LPS) was purified from Escherichia coli serotype 0127:B8 (obtained from Sigma [Code L3137]). A solution of LPS at a concentration of 0.5 mg/ml in sterile endotoxin free 0.9% saline (obtained from Flowfusor) was prepared. Two hours after the administration of the Test Compound, 0.2 ml of the LPS solution was administered intraperitoneally to each of the Test Mice. A control group of eight BALB/c mice (hereinafter referred to as the Control Mice) were treated in a similar manner to that described above for the Test Mice except that no Test Compound was included with the carrier. One hour after administration of LPS to the Control Mice and Test Mice, they were killed by rising concentration of CO_2 and blood samples were collected by cardiac puncture.

The blood was allowed to clot at room temperature for one hour and the serum was separated from the clotted blood following centrifugation. The serum was stored at -35°C until assay. Serum from individual mice at a dilution of 1:4 was assayed for TNF-α concentration by the enzyme linked immunosorbant assay (hereinafter referred to as ELISA) which was carried out as follows. Each well in a vinyl assay plate containing 96 wells (from Costar) was coated with 50 µl of 2 µg/ml hamster anti-mouse TNF-(α and β) monoclonal antibody in a 0.1M sodium hydrogen carbonate buffer at pH 8.2 and the plate was left overnight at 4°C. The plate was then washed

with a wash buffer (comprising phosphate buffered saline [hereinafter known as PBS] with 0.05% v/v of the sorbitan ester available commercially under the trade name Tween 20). Then a 200 µl aliquot of a blocking/dilution buffer (comprising 10% sheep serum in PBS with 0.1% v/v of the Tween 20 sorbitan ester) was added to each well and the plate was incubated at 37°C for 30 minutes. After aspirating the blocking buffer, the murine serum samples diluted 1:4 in the blocking/dilution buffer, or (as standards) purified recombinant murine TNF-α (obtained from Genzyme) at a range of concentrations, were added to duplicate wells and the plate was incubated at 37°C for a further two hours. The plate was washed with the wash buffer and 100 µl of a rabbit antibody solution (comprising a 1 in 10,000 dilution of a polyclonal rabbit anti-mouse TNF-α antibody in the blocking/dilution buffer [prepared as above]) was added to each well and incubated for a further 1 hour 30 minutes at 37°C. The plate was washed again and then 100 µl of an anti-rabbit IgG peroxidase conjugate (obtained from Binding Site) at a 1 in 4000 dilution was added to each well, and the plate was incubated at 37°C for 30 minutes. After further washing of the plate, 100 µl of a substrate solution was added to each well (the substrate solution comprised 0.1 mg/ml 3,3',5,5'-tetramethylbenzidine dihydrochloride buffered to pH 5.0 with a 0.1 M phosphate citrate buffer, to which 2 µl of 30% hydrogen peroxide per 10 ml was added just before use). The colour of the solution in each well was allowed to develop. The reaction was stopped by the addition of 25 µl of 1 M sulphuric acid and the optical density of the solution in each well read in a multichannel spectrophotometer at 450 mm.

The concentration (expressed as ng/ml) of TNF-α in the serum collected from each of the Test Mice was compared with that in the serum of each of the Control

Mice. The mean TNF-α serum concentration of the Test Mice and the Control Mice was determined by comparison with a standard curve. The significance of the percentage change of mean TNF-α serum concentration between the Test Mice and Control Mice was determined by one-way analysis of variance followed by a two-tailed multiple t-test. A reduction in serum TNF-α concentration between the Test Mice and Control Mice indicated that the Test Compound inhibited the release of mouse TNF-α, and thus had activity as an immunosuppressant. Test Compounds which caused a statistically significant percentage reduction of >35% in mean serum TNF-α concentration at a single dose of the Test Compound of 100 mg/kg or less were considered active in the MTNF Test. The lowest dose (minimum effective dose [MED]) for which activity was found was determined for each Test Compound.

The invention is illustrated by the following non-limitative Examples in which parts and percentages are by weight and compositions of mixed solvents are given by volume. Novel compounds were characterised by elemental analysis and one or more of the following spectroscopic techniques: nuclear magnetic resonance, infra-red and mass spectroscopy.

In the Examples the following abbreviations are used: IMS = industrial methylated spirit and DMF = N,N-dimethylformamide.

Unless otherwise stated, the starting materials used in the Examples are commercially available and may be obtained by reference to the Fine Chemicals Directory.

EXAMPLE 1

a) A mixture of 2-chloro-6-methylnicotinic acid (25.00 g) and 33% methylamine in ethanol (100 ml) was heated in a pressure vessel at 100°C for 18 hours. The mixture was cooled, diluted with water (200 ml) and acidified to pH 2-3 with concentrated hydrochloric acid. The mixture was cooled in an ice bath and filtered to give 6-methyl-2-methylaminonicotinic acid hemihydrochloride hydrate, m.p. 195-197°C.

b) Chloroacetonitrile (8.55 g) was added to a mixture of the product from a) (13.67 g), triethylamine (10.90 g) and acetone (200 ml) with stirring at 0°C. The resultant mixture was boiled under reflux for 18 hours. Additional triethylamine (5.45 g) and chloroacetonitrile (4.28 g) were added and the mixture was boiled under reflux for a further 6 hours. The mixture was allowed to stand at ambient temperature for 64 hours, then heated to boiling point, hot filtered and the filtrate evaporated to give a residue which was triturated with water and filtered to give cyanomethyl 6-methyl-2-methylaminonicotinate, m.p. 154-157°C.

c) A mixture of the product from b) (12.6 g), triethylamine (1.24 g) and methanol (100 ml) was boiled under reflux for 1 hour. Further methanol (50 ml) was added and the mixture was boiled under reflux for a further 18 hours. The mixture was allowed to stand at ambient temperature for 64 hours and then the solvent was evaporated under reduced pressure. The residue obtained was partitioned between dichloromethane and water. The organic layer was separated and evaporated to give methyl 6-methyl-2-methylaminonicotinate as an oil.

d) A mixture of the product from c) (2.00 g), selenium dioxide (3.00 g), pyridine (15 ml) and water (7.5 ml) was boiled and stirred under reflux for 6 hours and then allowed to stand at ambient temperature for 72 hours. Additional selenium dioxide (1.50 g) was added and the mixture was boiled under reflux for a further 4 hours. Pyridine (20 ml) was added. The mixture was boiled under reflux and then hot filtered. The residue was washed thoroughly with IMS and the combined filtrate and washings were evaporated under reduced pressure to give a brown solid which was stirred in water (40 ml) and 4M hydrochoric acid (10 ml) for 2 hours. The mixture was filtered and the collected solid was washed with water, dissolved in dichloromethane/methanol (10:1), dried, filtered and evaporated to give 5-methoxycarbonyl-6-methylaminopyridine-2-carboxylic acid, m.p. 152-153°C.

e) Ethyl malonyl chloride (2.60 g) was added to a mixture of the product from d) (1.80 g), triethylamine (1.73 g) and dichloromethane (100 ml). The mixture was allowed to stand at ambient temperature for 16 hours. The solvent was removed under reduced pressure and the residue was triturated with ether and filtered. The filtrate was evaporated and the residue obtained was dissolved in ethanol (50 ml). This solution was added to a solution of sodium ethoxide in ethanol prepared by dissolving sodium (0.8 g) in ethanol (80 ml). The mixture was stirred for 2 hours at ambient temperature and then water (250 ml) was added and the resultant solution was acidified to pH 1 with concentrated hydrochloric acid. The mixture was stirred for 30 minutes and the precipitate collected by filtration and dried under vacuum at 60°C to give 6-ethoxycarbonyl-5-hydroxy-8-methyl-7-oxo-7,8-dihydro-1,8-naphthyridine-2-carboxylic acid, m.p. 250-253°C (with decomposition).

f) A mixture of the product from e) (3.10 g), ethanol (400 ml) and p-toluenesulphonic acid (0.30 g) was boiled under reflux through a Soxhlet condenser containing molecular sieves for 20 hours. The mixture was cooled in an ice bath and filtered to give diethyl 5-hydroxy-8-methyl-7-oxo-7,8-dihydro-1,8-naphthyridine-2,6-dicarboxylate, m.p. 174-175°C.
Active 2/2 at 30 mg/kg;
Active 1/2 at 10 mg/kg.

PHARMACEUTICAL EXAMPLES

Example U

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 10 mg active compound.

Example V

Tablets are prepared from the following ingredients.

	Parts by Weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone

in ethanol. The dry granulate is blended with magnesium stearate and the rest of the starch. The mixture is then compressed in a tableting machine to give tablets containing 10 mg of active compound.

Example W

Tablets are prepared by the method of the previous Example. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

Example X

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of semi-synthetic glycerides as the suppository base and the mixture formed into suppositories each containing 100 mg of active ingredient.

Example Y

In the preparation of capsules, 50 parts by weight of active compound, 300 parts by weight of lactose and 3 parts by weight of magnesium stearate are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 50 mg of active ingredient.

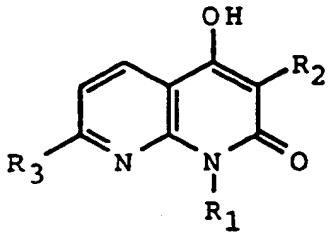
Example Z

The active compound is incorporated into the base by thorough homogenization until the drug is evenly distributed. The ointment is packed into 10 g amber jars with screw-capped lined lids.

Active compound	0.1 g
White soft paraffin to	10 g

CLAIMS

1. Compounds of formula I



I

including pharmaceutically acceptable salts thereof in which

R_1 represents a C_{1-6} alkyl group;

R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-5} alkyl group; and

R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-5} alkyl group.

2. Compounds according to claim 1 in which

R_1 represents a C_{1-2} alkyl group; and

R_2 and R_3 are identical and represent a C_{2-4} alkoxycarbonyl group.

3. A compound according to claim 1 which is diethyl 5-hydroxy-8-methyl-7-oxo-7,8-dihydro-1,8-naphthyridine-2,6-dicarboxylate.

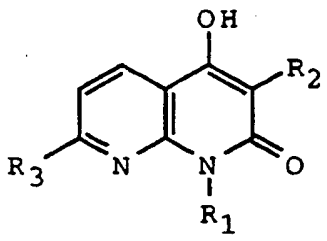
4. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in any one of claims 1-3 together with a pharmaceutically acceptable diluent or carrier.

5. The use of a compound as claimed in any one of claims 1-3 as a medicament.

6. The use of a compound as claimed in any one of claims 1-3 in the treatment of rheumatic diseases.

7. The use of a compound as claimed in any one of claims 1-3 in the treatment of diseases resulting from an aberrant immune reaction.

8. A method of treating rheumatic diseases comprising the administration of a therapeutically effective amount of a compound of formula I



I

including pharmaceutically acceptable salts thereof in which

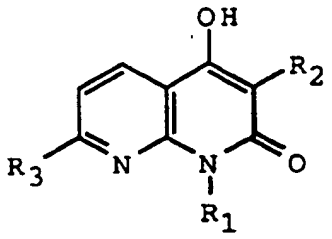
R_1 represents a C_{1-6} alkyl group;

R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-5} alkyl group; and

R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-5} alkyl group;

to a mammal in need thereof.

9. A method of treating diseases with an immunological association comprising the administration of a therapeutically effective amount of a compound of formula I



I

including pharmaceutically acceptable salts thereof in which

R_1 represents a C_{1-6} alkyl group;

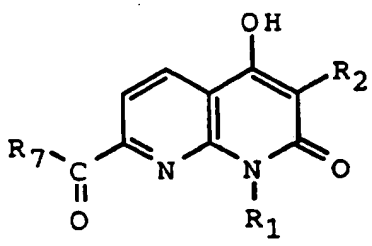
R_2 represents a group of formula $COOR_4$ in which R_4 represents a C_{1-5} alkyl group; and

R_3 represents a group of formula $COOR_5$ in which R_5 represents a C_{1-5} alkyl group;

to a mammal in need thereof.

10. A process to prepare a compound of formula I as claimed in claim 1 comprising:

a) reacting a compound of formula IIa

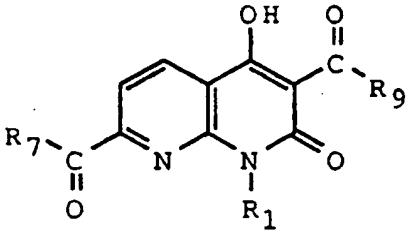


IIa

in which R_1 and R_2 are as previously defined and R_7 represents a leaving group with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, optionally in the presence of an inert organic liquid and optionally when R_7 represents halo in the presence of a base: or

b) reacting a compound of formula IIa in which R_1 and R_2 are as previously defined and R_7 represents hydroxy with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, optionally in the presence of an inert organic liquid and/or in the presence of: a) an acid catalyst; or b) a dehydrating agent; or c) an organic liquid which provides a method of water removal by formation of an azeotrope; or

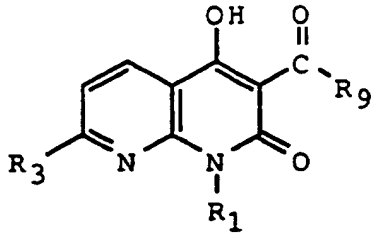
c) reacting a compound of formula IIb



IIb

in which R_1 is as previously defined and R_7 and R_9 independently represent a) a leaving group or b) hydroxy, with an alcohol of formula R_4OH in which R_4 represents a C_{1-5} alkyl group at a temperature in the range -50 to 250°C, optionally when R_7 and/or R_9 represents halo in the presence of an inert organic liquid and/or in the presence of a base, and optionally: when R_7 and/or R_9 represents hydroxy in the presence of an inert organic liquid and/or in the presence of: a) an acid catalyst; or b) a dehydrating agent; or c) an organic liquid which provides a method of water removal by formation of an azeotrope; to give compounds of formula I in which R_2 and R_3 are identical and represent a group of formula $COOR_4$ as previously defined;

d) reacting a compound of formula IIc

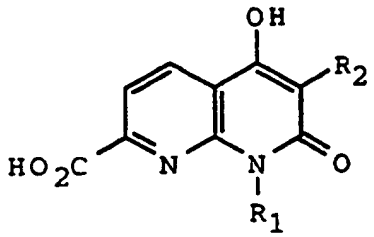


IIc

in which R_1 and R_3 are as previously defined and R_9 represents a leaving group with an alcohol of formula R_4OH, in which R_4 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, and optionally in the presence of an inert organic liquid and optionally when R_9 represents halo in the presence of a base; or

e) reacting a compound of formula IIc in which R_1 and R_3 are as previously defined and R_9 represents hydroxy, at a temperature in the range -50 to 250°C, optionally in the presence of an inert organic liquid, and/or in the presence of: a) an acid catalyst; or b) a dehydrating agent; or c) an organic liquid which provides a method of water removal by formation of an azeotrope; or

f) reacting a compound of formula IId

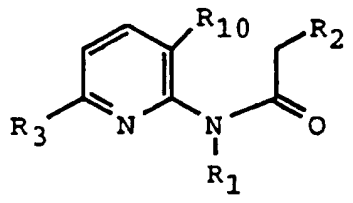


IId

in which R_1 and R_2 are as previously defined with an alcohol of formula R_5OH, in which R_5 represents a C_{1-5} alkyl group, at a temperature in the range -50 to 250°C, optionally in the presence of an inert organic liquid in the presence of: a) an acid catalyst; or b) a

dehydrating agent; or c) an organic liquid which provides a method of water removal by formation of an azeotrope; or

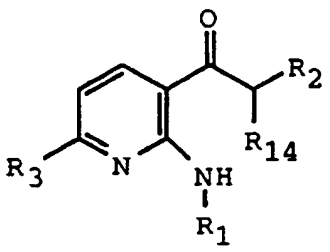
g) cyclising a compound of formula III



III

in which R_1, R_2 and R_3 are as initially defined and R_{10} represents cyano or a group of formula COR_{11} in which R_{11} represents a leaving group, in the presence of a base, in the presence of an inert organic liquid, at a temperature in the range -50 to 250°C, optionally followed by hydrolysis when R_{10} represents cyano and optionally followed by acidification; or

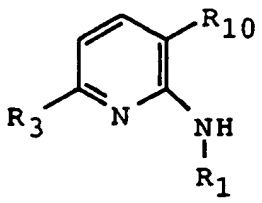
h) cyclising a compound of formula IV



IV

in which R_1, R_2 and R_3 are as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously defined, by heating, at a temperature in the range 30-250°C in the presence of an inert organic liquid; or

i) condensing a compound of formula V



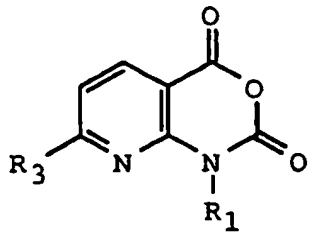
V

in which R_1, R_3 and R_{10} are as initially defined with a compound of formula VI

$$R_2CH_2R_{14} \qquad VI$$

in which R_2 is as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously defined, by reacting together at a temperature in the range 0-150°C, in the presence of a base, in the presence of an inert organic liquid and then reacting at a temperature in the range 0-250°C, optionally followed by hydrolysis when R_{10} represents cyano and optionally followed by acidification;

j) reacting a compound of formula VII



VII

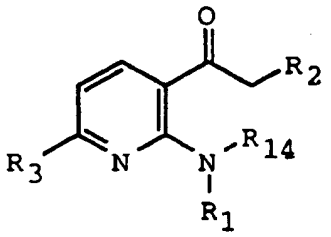
in which R_1 and R_3 are as initially defined with a compound of formula VI

$$R_2CH_2R_{14} \qquad VI$$

in which R_2 is as initially defined and R_{14} represents a group of formula COR_{11} in which R_{11} is as previously

defined, by reacting together at a temperature in the range 0-150°C, in the presence of a base, in the presence of an inert organic liquid, and then reacting at a temperature in the range 0-250°C, optionally followed by acidification; or

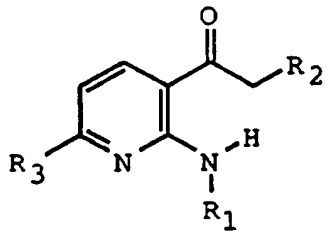
k) cyclising a compound of formula IX



IX

in which R_1, R_2, R_3 and R_{14} are as previously defined, optionally in the presence of a base, in the presence of an organic liquid, at a temperature in the range 0-150°C optionally followed by acidification; or

l) reacting a compound of formula XIII

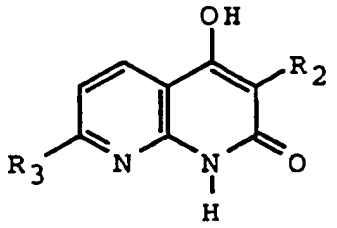


XIII

in which R_1, R_2 and R_3 are as initially defined with a compound of formula Y_1COY_2 in which Y_1 represents halo, alkoxy (optionally substituted by halo), aryloxy, arylalkoxy, cyano or a group of formula $NR_{15}R_{16}$ (in which R_{15} and R_{16} independently represent a C_{1-6} alkyl group or R_{15} and R_{16} together with the nitrogen atom to which they are attached represent a saturated 3-7 membered heterocyclic ring) and Y_2 represents halo,

alkoxy (optionally substituted by halo), aryloxy or arylalkoxy, optionally in the presence of a base, in the presence of an inert organic liquid at a temperature in the range 0-150°C; or

m) reacting a compound of formula XII



XII

in which R_2 and R_3 are as initially defined, with an alkylating agent of formula R_1X in which R_1 is as previously defined and X represents a leaving group.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/03769

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 452 873 (KYOWA) 23 October 1991 cited in the application see page 3, line 1 - line 2; claim 1	1,4
A,P	WO,A,95 07909 (BOOTS) 23 March 1995 see claims 1,11	1,4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 1996	29 -01- 1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/ 03769

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark : Although claims 8 and 9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/ composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter nal Application No
PC1/EP 95/03769

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-452873	23-10-91	JP-A-	4217981	07-08-92
		US-A-	5126341	30-06-92
WO-A-9507909	23-03-95	AU-B-	7695094	03-04-95